

**Comments and Recommended Revisions/Corrects for: Guidance for Industry and FDA Staff, Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Document issued on: January 13, 2005**

**Comments provided by:**

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Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

**Page 19, Document Statements**

**11. Magnetic Resonance Imaging (MRI) Safety and Compatibility**

**Significance**

MRI of patients with stents poses the following potential hazards:

- heating of the implant and subsequent tissue damage
- movement of the implant, resulting in tissue damage or misplacement
- imaging difficulties resulting in inappropriate medical treatment.

In addition, we are concerned that a large population of patients may receive inadequate treatment if radiologists choose not to perform MRI on a patient because of their uncertainty about the possibility of migration in a stent with characteristics that may affect time to endothelialization.

**Recommendation**

FDA recommends that you address the issues affecting safety and compatibility of your stent in the MRI environment as described below.

**Comment:**

This section refers to MRI Safety and Compatibility. Here and throughout this document,

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reference is made to these terms, which are used in an interchangeable manner without distinction. This is problematic insofar as the terms "MR-safe" and "MR-compatible" have been defined by various ASTM documents, as follows:

*MR-safe*—the device, when used in the MR environment, has been demonstrated to present no additional risk to the patient or other individuals, but may affect the quality of the diagnostic information. The MR conditions in which the device was tested should be specified in conjunction with the term MR safe since a device which is safe under one set of conditions may not be found to be so under more extreme MR conditions.

*MR-compatible*—the device, when used in the MR environment, is MR-safe and has been demonstrated to neither significantly affect the quality of the diagnostic information nor have its operations affected by the MR device. The MR conditions in which the device was tested should be specified in conjunction with the term MR-compatible since a device which is compatible under one set of conditions may not be found to be so under more extreme MR conditions.

As such, this section as well as other parts of this document should be revised, accordingly. Importantly, I strongly feel that these corrections should be made in a timely manner by the FDA in order to avoid undue confusion by stent and other implant manufacturers, as well as those in the MRI community.

#### **Page 20, Document Statement:**

##### **Test Environment**

We recommend that you report details of the test environment, such as, but not limited to:

- magnetic field strength in Tesla (T)
- spatial gradient
- time rate of change of magnetic field (dB/dt)
- specific absorption rate (SAR).

We recommend that you use the highest widely available field strength (currently 3T) and worst case conditions for your testing. As systems with higher field strengths become available, we recommend they be used as the most current worst case.

##### **Comment:**

The time rate of change of magnetic field (dB/dt) is not known to impact the safety of a patient with a stent undergoing MRI. Therefore, it is unnecessary to provide details pertaining to this to the FDA (unless the FDA can provide guidance with regard to how the dB/dt affects MR safety for a stent).

Also, this document recommends that, "you use the highest widely available field strength (currently 3-T). Presently, over 18,000 MR systems exist in the world. Less than 300 operate at 3-Tesla (less than 2%). As such, 3-T scanners are not widely used. The highest widely available field strength is 1.5-Tesla. Please revise, accordingly.

## Page 31, Document Statement

### F. MRI Compatibility

We recommend that your labeling contain information for the patient and medical personnel about any potential hazards that MRI may present as a result of the implanted stent. We recommend that labeling describing the MRI compatibility of your stent be based on whether you have tested the effects of force, torque, and radiofrequency (RF) heating in the MRI environment. For the recommended testing, see section VII. Non-Clinical Tests, B. Stent Dimensional and Functional Attributes, 11. Magnetic Resonance Imaging (MRI) Safety and Compatibility.

#### Stents Tested for Force, Torque, and Heating

If you have tested for force, torque, and heating, successfully, we recommend that your labeling describe the testing and results, for example:

Through non-clinical testing, the ABZ stent has been shown to be MRI safe at field strengths of x Tesla or less and a maximum whole body averaged specific absorption rate (SAR) of y for z min of MRI. The ABZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

In this testing, the stent produced a temperature rise of less than x degrees C at a maximum whole body averaged specific absorption rate (SAR) of x W/kg for z minutes of MRI.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

#### Comment:

Again, incorrect or confusing terminology is used in this section. That is, the terms MRI safe (MR-safe) and MR compatibility (MR-compatible) are used interchangeably. Please revise this document to state the correct term, "MR-safe".

## Pages 31, 32 Document Statement

### Overlapping Stents or Stents with Fractured Struts

In addition to the above description of force, torque, and heating testing on the stent, FDA recommends that your labeling also describe whether you determined the effect of heating in the MRI environment for overlapping stents or stents with fractured struts. If you have not determined what those effects are, we recommend that your labeling reflect this, for example: The effect of heating in the MRI environment for overlapping stents or stents with fractured struts is not known.

**Comment:**

While overlapping stents that contact one another effectively increase the overall stent length and, as such, may impact heating, there is no evidence that “fractured struts” produce a different heating profile compared to stents with normal struts. Therefore, it is inappropriate to recommend a statement like this in the labeling of stents, especially since it may prevent a patient from undergoing an MRI procedure. [For example, consider the scenario of an over-cautious MRI user thinking that this statement suggests that a safety issue may exist for a stent with a fractured strut and having no way of knowing whether fractured struts exist for the stent or not.] Therefore, I highly recommend that this section undergo revision to delete reference to a “fractured strut” suggesting that it may impact MR safety.

Furthermore, besides using overlapped stents, stents may be utilized as “stacked”, “sandwiched” or in such a manner that MRI-related heating may be substantially different compared to what occurs for a single stent. If these other uses are anticipated, the FDA should recommend additional testing for MRI-related heating.

See references:

Sandwich Di Mario C, Marsico F, Adamian M, Karvouni E, Albiero R, Colombo A. New recipes for in-stent restenosis: cut, grate, roast, or sandwich the neointima? Heart. 2000 Nov;84(5):471-5.

Pienvichit P, Waters J. Successful closure of coronary artery perforation using makeshift stent sandwich. Catheter Cardiovasc Interv. 2001

**Page 32 Document Statement**

**Drug-Eluting Stents not Tested for Heating**

If you have determined the **MRI compatibility** of your stent with force and torque tests, but do not have heating test data, we recommend your labeling advise users of this, for example:

Non-clinical testing at field strengths of x T or less showed that the XYZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

**Comment:**

Again, incorrect or confusing terminology is used in this section. Please revise this document to state the correct term, “MR-safe”.

## Page 33 Document Statement

### Literature Review with No Testing for 316L Stainless Steel or Nitinol Stents

For a 316L stainless steel or nitinol stent, if you have not conducted testing for migration or heating, but have provided comparisons to published test results in your PMA, your labeling should reflect that MRI compatibility is based on literature, for example:

Although comparisons to published test results indicate that the YZX stent may not migrate in the MRI environment at field strengths of x T or less, the YZX stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel (or nitinol) stent, this period is usually considered to be 8 weeks.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

We recommend basing your MRI compatibility labeling on testing instead of literature for drug-eluting stents or stents with indications where MRI is used to rule out common adverse events, for example, carotid stenting where MRI is used to look for strokes shortly after implantation. FDA believes that you should perform MRI compatibility testing for these stents to ensure that these patients are not refused medically-indicated MRI scans because the stent labeling indicates a lack of MRI compatibility testing.

#### **Comment:**

(a) Again, incorrect or confusing terminology is used in this section. Please revise this document to state the correct term, "MR-safe".

(b) This document appears to erroneously indicate that patients with nitinol or 316L stainless steel stents should wait 8 weeks before undergoing an MRI procedure. There is a large body of data in the peer-reviewed literature that supports the fact that stents made from nitinol and 316L stainless steel do not present issues with regard to magnetic field interactions.

Of note is that the recommended labeling information for an implant made from 316L stainless steel or nitinol with MR safety *conflicts* with published reports for various implants made from these materials, including recent work performed on coronary stents made from 316L stainless steel (Hug et al). To date, no stent made from 316L stainless steel has been observed to display magnetic field interactions at 1.5-Tesla.

- Shellock FG, Shellock VJ. Stents: Evaluation of MRI safety. *AJR American Journal of Roentgenology* 1999;173:543-547.
- Shellock, FG. Reference manual for magnetic resonance safety, implants, and devices: 2005 edition. Biomedical Research Publishing Group, Los Angeles, CA, 2005.
- Shellock FG. Biomedical implants and devices: assessment of magnetic field interactions with a 3.0-Tesla MR system. *J Magn Reson Imaging* 2002;16:721-732.
- Hug J, Nagel E, Bornstedt A, Schackenburg B, Oswald H, Fleck E. Coronary arterial stents: safety and artifacts during MR imaging. *Radiology* 2000;216:781-787.

Therefore, I highly recommend that this statement undergo substantial revision. For example, perhaps the example of a stent made from 304 stainless steel should be used.

Please note that I am aware of at least two cases that have resulted in legal action where a patient needed an emergent MRI and was required (inappropriately) to wait a 6 to 8 week period due to the presence of an implant.

### **Page 33 Document Statement**

#### **Modified Stainless Steel Stents with Unchanged Cold Work**

If you demonstrate that the amount of cold work in your modified stainless steel stent has not significantly changed from a design used in an approved stent, you should label the stent to indicate that while the stent has not been tested, it is comparable to previous devices, for example:

Although comparisons to other devices marketed in the US indicate that the X stent may not migrate in the MRI environment at field strengths of x T or less, the XYZ stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel stent, this period is usually considered to be 8 weeks. This device has not been evaluated for heating in the MRI environment. MRI image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

#### **Comments:**

Again, this document erroneously indicates that a patient with a 316L stainless steel stent needs to wait 8 weeks before undergoing an MRI procedure. I highly recommend that this statement undergo revision. For example, perhaps the example of a stent made from 304 stainless steel should be used.

### **Page 34 Document Statement**

#### **Modified Stainless Steel Stents with Modified Cold Work**

If the amount of cold work in your stent has significantly increased from a design used in an approved stent, we recommend that you perform appropriate testing as

described in section VII. **Non-Clinical Tests, B. Stent Dimensional and Functional Attributes, 11. Magnetic Resonance Imaging (MRI) Safety and Compatibility** and describe the results in your labeling, for example:

Non-clinical testing at field strengths of x T or less showed that the XYZ stent should not migrate in this MRI environment. Non-clinical testing has not been performed to rule out the possibility of stent migration at field strengths higher than x Tesla.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

**Comment:**

Incorrect terminology is used in this section. Please revise this document to state the correct term, "MR-safe".

**Page 34 Document Statement**

**No Literature Review and No Testing – 316L or Nitinol**

If you have not tested your 316L or nitinol stent or compared it to published literature, we recommend your labeling reflect this, for example:

The ABC stent has not been tested for safety in the MRI environment. Therefore, MRI scans should not be performed on patients post-implantation until the stent has completely endothelialized to minimize the potential for migration. For a conventional uncoated 316L stainless steel (or nitinol) stent, this period is usually considered to be 8 weeks.

This device has not been evaluated for heating in the MRI environment.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the stent.

As stated above, we recommend basing your MRI compatibility labeling on testing instead of literature to ensure that certain patients are not refused medically indicated MRI scans because the stent labeling indicates a lack of MRI compatibility testing.

**Comments:**

(a) This document erroneously indicates that a patient with a 316L stainless steel stent needs to wait 8 weeks before undergoing an MRI procedure. I highly recommend that this statement undergo revision. For example, perhaps the example of a stent made from 304 stainless steel should be used.

(b) Incorrect terminology is used in this section. Please revise this document to state the

correct term, "MR-safe".

## Page 34 Document Statement

### **MRI Compatibility Based on Animal Testing**

If you have performed animal testing that shows that your stent does not damage tissue at a specific SAR, your labeling should reflect this, for example:

Animal histology results for the X stent showed no significant tissue damage at a maximum whole body average specific absorption rate (SAR) of x W/kg for z minutes of MRI.

However, if you did not assess the effect of heating on the drug or polymer coating of a drug-eluting stent, your labeling should reflect this, for example:

Animal histology results for the X stent showed no significant tissue damage at a maximum whole body average specific absorption rate (SAR) of x W/kg for z minutes of MRI. The effect of heating in the MRI environment for overlapping stents or stents with fractured struts is not known. The effect of heating in the MRI environment on the drug or polymer coating is not known.

### **Comments:**

Incorrect terminology is used in this section. Please revise this document to state the correct term, "MR-safe". Also, reference to the issue of stents with fractured struts should be reconsidered.

## Appendix A, Document Statement

### **Appendix A: Test Summary Checklist** (continued on next page)

Test		Sizes Tested and Sample Sizes	Test Method or Standard Reference	Accept
Material Characterization	Material Composition			
	Shape Memory and Superelasticity			
	Mechanical Properties			
	Corrosion Resistance			
Stent Dimensional and Functional Attributes	Dimensional Verification			
	Percent Surface Area of the Stent			
	Foreshortening			
	Recoil for Balloon Expandable Stents			
	Stent Integrity			



	Radial Stiffness and Radial Strength			
	Stress Analysis			
	Fatigue Analysis			
	Accelerated Durability Testing			
	MRI Safety and Compatibility			
	Radiopacity			
	Coating Durability ( <i>coated stents only</i> )			
	Crush Resistance ( <i>peripheral indications only</i> )			
	Kink Resistance ( <i>peripheral indications only</i> )			

**Comments:**

Incorrect terminology is used in this section. Please revise this document to state the correct term, "MR-safe".



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